PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 215/26, A61K 31/47 — A1

(11) International Publication Number: WO 98/57936

(43) International Publication Date: 23 December 1998 (23.12.98)

(21) International Application Number: PCT/GB98/01770

(22) International Filing Date: 17 June 1998 (17.06.98)

(30) Priority Data:
9712761.7 17 June 1997 (17.06.97) GB

(71) Applicant: DARWIN DISCOVERY LIMITED [GB/GB]; Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB).

(72) Inventors: DYKE, Hazel, Joan; Darwin Discovery Limited, Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB). MONTANA, John, Gary; Darwin Discovery Limited, Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB). HAUGHAN, Alan, Findlay; Darwin Discovery Limited, Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB). SABIN, Verity, Margaret; Darwin Discovery Limited, Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB).

(74) Agent: GILL JENNINGS & EVERY; Broadgate House, 7 Eldon Street, London EC2M 7LH (GB).

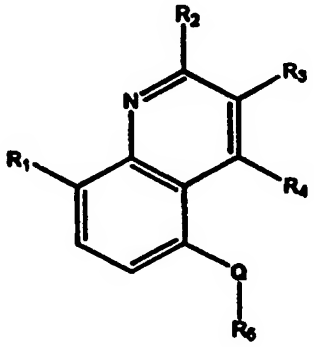
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: QUINOLINE DERIVATIVES AS PDE IV AND/OR TNF INHIBITORS

(57) Abstract

Compounds of formula (i) wherein R_1 represents C_{1-6} alkoxy (alkyl portion optionally substituted with one or more halogens) or thioalkyl; Q represents an aryl or heteroaryl ring, attached through any appropriate atom and optionally substituted at any position(s) with one or more substituents R_5. The compounds can be used to treat disease states, for example disease states associated with proteins that mediate cellular activity, for example by inhibiting tumour necrosis factor and/or by inhibiting phosphodiesterase IV.



(i)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

QUINOLINE DERIVATIVES AS PDE IV AND/OR TNF INHIBITORS

Field of the Invention

The present invention relates to novel quinolines, and to their formulation and use as pharmaceuticals.

Background of the Invention

Japanese Patent Publication 2-184673 discloses quinolinesulphonamides.

US-A-4910193 discloses quinolinesulphonamides, in which the sulphonamide nitrogen is substituted by a variety of bridged saturated ring systems, as medicaments suitable for the treatment of serotonin-induced gastrointestinal disturbances.

US-A-4857301 and US-A-5340811 disclose quinolinesulphonamides in the treatment of asthma, respectively as bronchodilators and as anti-allergic compounds.

Trecourt *et al*, J. Het. Chem. (1995) 32 1261, describe the preparation of 5-arylquinolines as intermediates for the synthesis of pyridocarbazoles. Trecourt *et al*, *Syn. Commum.* (1995) 25 4011, describe 5-phenylquinolines as intermediates for the synthesis of indoloquinolines.

5-Heteroarylquinolines and 5-heterocycloquinolines with anti-microbial activity are described by Khalil *et al*, J. Indian Chem. Soc. (1987) LXIV 42, and *ibid* (1990) 67 821.

A series of patents by Bayer (including US-A-5304563, EP-A-0582908 and EP-A-0545170) discloses 2-substituted quinolines, including 5-arylquinolines, as lipoxygenase inhibitors.

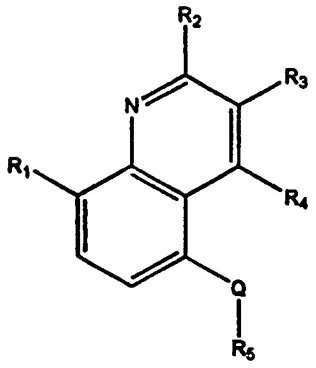
Phosphodiesterases (PDE) and Tumour Necrosis Factor (TNF), their modes of action and the therapeutic utilities of inhibitors thereof, are described in WO-A-9636595, WO-A-9636596 and WO-A-9636611, the contents of which are incorporated herein by reference. The same documents disclose sulphonamides having utility as PDE and TNF inhibitors.

Certain quinolines are known, without associated therapeutic activity. These include 5,5'-bis(8-methoxyquinoline), 5,5'-bis(8-methoxyquinaldine), 1-(8-ethoxy-5-quinolyl)-3,4-dihydroisoquinoline, 1-(8-ethoxy-5-quinolyl)isoquinoline, 2-(8-ethoxy-5-quinolyl)-1,2,3,4-tetrahydroisoquinoline, 8-isopropoxy-5-(1-naphthyl)quinoline, 5-methoxy-8-phenylquinoline, 5-methoxy-8-[2-(t-butylcarbonylamino)phenyl]quinoline and 5-methoxy-8-[2-(t-butylcarbonylamino)-5-methoxyphenyl]quinoline. See Chem. Abs. (1962) 57(9):11159e; Chem. Abs. (1963) 59(6):6364e; Beugelmans & Bois-Chaussy, J.

Org. Chem. (1991) 56:2518-2522; and Trécourt *et al*, J. Heterocyclic Chem. (1995) 32:1261.

Summary of the Invention

This invention is based on the discovery of novel compounds that can be used to treat disease states, for example disease states associated with proteins that mediate cellular activity, for example by inhibiting tumour necrosis factor and/or by inhibiting phosphodiesterase IV. According to the invention, the novel compounds are of formula (i):



(i)

R_1 represents C_{1-6} alkoxy (alkyl portion optionally substituted with one or more halogens), OH or thioalkyl;

R_2, R_3 and R_4, which may be the same or different, represent H, OR_{11}, COR_7, CN, CO_2R_8, $C(=NOR_7)R_7$, alkyl-$C(=NOR_7)R_7$, halogen, CF_3, $CONR_{12}R_{13}$, NR_9R_{10} or R_7;

R_5 represents halogen, arylalkyl, heteroarylalkyl, heterocycloalkyl, alkyl, hydroxy, alkoxy, CO_2R_8, $SO_2NR_{12}R_{13}$, $CONR_{12}R_{13}$, CN, NR_9R_{10}, COR_{11} or $S(O)_nR_{11}$;

R_7 represents H, alkyl, cycloalkyl, aryl, heteroaryl, heterocyclo, arylalkyl, heteroarylalkyl or heterocycloalkyl, any of which may be optionally substituted at any position with R_{16};

R_8 represents H, alkyl, arylalkyl, heteroarylalkyl or heterocycloalkyl;

R_9 represents alkylcarbonyl, alkoxycarbonyl, arylsulphonyl, heteroarylsulphonyl, heterocyclosulphonyl, arylcarbonyl, heteroarylcarbonyl, heterocyclocarbonyl or alkylsulphonyl and R_{10} represents H or R_{11}, or NR_9R_{10} represents a heterocyclic ring (such as morpholine or piperidine) optionally substituted with one or more R_{15};

R_{11} represents alkyl, cycloalkyl, aryl, heteroaryl, heterocyclo, arylalkyl, heteroarylalkyl or heterocycloalkyl;

R_{12} and R_{13}, which may be the same or different, each represent R_7, or $NR_{12}R_{13}$ represents a heterocyclic ring (such as morpholine or piperidine) optionally substituted with one or more R_{15};

R_{15} represents alkyl, arylalkyl or heteroarylalkyl;

R_{16} represents halogen, hydroxy, OR_{11}, NR_9R_{10}, CN, CO_2H, CO_2R_{11}, $CONR_{12}R_{13}$ or COR_{11};

n represents 0-2; and

Q represents an aryl or heteroaryl ring, attached through any appropriate atom and optionally substituted at any position(s) with one or more substituents R_5;

and pharmaceutically-acceptable salts thereof.

Combinations of substituents and/or variables are only permissible if such combinations result in stable compounds.

Description of the Invention

Suitable pharmaceutically-acceptable salts are pharmaceutically-acceptable base salts and pharmaceutically-acceptable acid addition salts. Certain of the compounds of formula (i) which contain an acidic group form base salts. Suitable pharmaceutically-acceptable base salts include metal salts, such as alkali metal salts for example sodium salts, or organic amine salts such as that provided with ethylenediamine.

Certain of the compounds of formula (i) which contain an amino group form acid addition salts. Suitable acid addition salts include pharmaceutically-acceptable inorganic salts such as the sulphate, nitrate, phosphate, borate, hydrochloride and hydrobromide and pharmaceutically-acceptable organic acid addition salts such as acetate, tartrate, maleate, citrate, succinate, benzoate, ascorbate, methanesulphate, α-ketoglutarate, α-glycerophosphate and glucose-1-phosphate. The pharmaceutically-acceptable salts of the compounds of formula (i) are prepared using conventional procedures.

It will be appreciated by those skilled in the art that some of the compounds of formula (i) may exist in more than one tautomeric form. This invention extends to all tautomeric forms.

It will be appreciated that the compounds according to the invention can contain one or more asymmetrically substituted atoms. The presence of one or more of these

asymmetric centers in a compound of formula (i) can give rise to stereoisomers, and in each case the invention is to be understood to extend to all such stereoisomers, including enantiomers and diastereoisomers, and mixtures including racemic mixtures thereof.

When used herein the term alkyl whether used alone or when used as a part of another group includes straight and branched chain alkyl groups containing up to 6 atoms. Alkoxy means an alkyl-O- group in which the alkyl group is as previously described. Aryloxy means an aryl-O- group in which the aryl group is as defined below. Heteroaryloxy means a heteroaryl-O- group and heterocyclooxy means a heterocyclo-O- group in which the heteroaryl and heterocyclo group are as defined below. Alkylamino means an alkyl-N- group in which the alkyl group is as previously defined, arylamino means aryl-N- and heteroarylamino means an heteroaryl-N- group (aryl and heteroaryl defined below). Cycloalkyl includes a non-aromatic cyclic or multicyclic ring system of about 3 to 10 carbon atoms. The cyclic alkyl may optionally be partially unsaturated. Aryl indicates carbocyclic radicals containing about 6 to 10 carbon atoms. Arylalkyl means an aryl-alkyl- group wherein the aryl and alkyl are as described herein. Heteroarylalkyl means a heteroaryl-alkyl group and heterocycloalkyl means a heterocyclo-alkyl group. Alkylcarbonyl means an alkyl-CO- group in which the alkyl group is as previously described. Arylcarbonyl means an aryl-CO- group in which the aryl group is as previously described. Heteroarylcarbonyl means a heteroaryl-CO- group and heterocyclocarbonyl means a heterocyclo-CO- group. Arylsulphonyl means an aryl-SO_2- group in which the aryl group is as previously described. Heteroarylsulphonyl means a heteroaryl-SO_2- group and heterocyclosulphonyl means a heterocyclo-SO_2- group. Alkoxycarbonyl means an alkyloxy-CO- group in which the alkoxy group is as previously desribed. Alkylsulphonyl means an alkyl-SO_2- group in which the alkyl group is as previously described. Carbonyl oxygen means a -CO- group. It will be appreciated that a carbonyl oxygen cannot be a substituent on an aryl or heteroaryl ring. Heterocyclic ring means about a 5 to about a 10 membered monocyclic or multicyclic ring system (which may be saturated or partially unsaturated) wherein one or more of the atoms in the ring system is an element other than carbon chosen from amongst nitrogen, oxygen or sulphur atoms. Examples include morpholine and piperidine. Heteroaryl means about a 5 to about a 10 membered aromatic monocyclic or multicyclic hydrocarbon ring system in which one or more of the atoms in the ring system is an element other than carbon, chosen from amongst nitrogen, oxygen

or sulphur; if desired, a N atom may be in the form of an N-oxide. Heterocyclo means about a 5 to about a 10 membered saturated or partially saturated monocyclic or multicyclic hydrocarbon ring system in which one or more of the atoms in the ring system is an element other than carbon, chosen from amongst nitrogen, oxygen or sulphur. Halogen means fluorine, chlorine, bromine or iodine.

Compounds of the invention are useful for the treatment of TNF mediated disease states. "TNF mediated disease or disease states" means any and all disease states in which TNF plays a role, either by production of TNF itself, or by TNF causing another cytokine to be released, such as but not limited to IL-1 or IL-6. A disease state in which IL-1, for instance, is a major component, and whose production or action is exacerbated or secreted in response to TNF, would therefore be considered a disease state mediated by TNF. As TNF-β (also known as lymphotoxin) has close structural homology with TNF-α (also known as cachectin), and since each induces similar biologic responses and binds to the same cellular receptor, both TNF-α and TNF-β are considered to be inhibited by compounds of the present invention and thus are herein referred to collectively as "TNF" unless specifically indicated otherwise.

This invention relates to a method for mediating or inhibiting the enzymatic activity or catalytic activity of PDE IV in a mammal in need thereof and for inhibiting the production of TNF in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of Formula (i) or a pharmaceutically-acceptable salt thereof.

PDE IV inhibitors are useful in the treatment of a variety of allergic and inflammatory diseases, including: asthma, chronic bronchitis, chronic obstructive airways disease, atopic dermatitis, atopic eczema, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, inflammation of the eye, allergic responses in the eye, eosinophilic granuloma, psoriasis, Bechet's disease, erythematosis, anaphylactoid purpura nephritis, joint inflammation, arthritis, rheumatoid arthritis and other arthritic conditions such as rheumatoid spondylitis and osteoarthritis, septic shock, sepsis, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxic shock and adult respiratory distress syndrome. In addition, PDE IV inhibitors are useful in the treatment of diabetes insipidus and conditions associated with cerebral metabolic inhibition, such as cerebral senility, senile dementia (Alzheimer's disease),

memory impairment associated with Parkinson's disease, depression and multi-infarct dementia. PDE IV inhibitors are also useful in conditions ameliorated by neuroprotectant activity, such as cardiac arrest, stroke and intermittent claudication. PDE IV inhibitors may be useful in the treatment of tardive dyskinesia, ischaemia and Huntingdon's disease. Additionally, PDE IV inhibitors could have utility as gastroprotectants. A special embodiment of the therapeutic methods of the present invention is the treatment of asthma.

The viruses contemplated for treatment herein are those that produce TNF as a result of infection, or those which are sensitive to inhibition, such as by decreased replication, directly or indirectly, by the TNF inhibitors of Formula (i). Such viruses include, but are not limited to HIV-1, HIV-2 and HIV-3, cytomegalovirus (CMV), influenza, adenovirus and the Herpes group of viruses, such as, but not limited to, *Herpes zoster* and *Herpes simplex*.

This invention more specifically relates to a method of treating a mammal, afflicted with a human immunodeficiency virus (HIV), which comprises administering to such mammal an effective TNF inhibiting amount of a compound of Formula (i) or a pharmaceutically-acceptable salt thereof.

The compounds of this invention may also be used in association with the veterinary treatment of animals, other than humans, in need of inhibition of TNF production. TNF mediated diseases for treatment, therapeutically or prophylactically, in animals include disease states such as those noted above, but in particular viral infections. Examples of such viruses include, but are not limited to feline immunodeficiency virus (FIV) or other retroviral infection such as equine infectious anaemia virus, caprine arthritis virus, visna virus, maedi virus and other lentiviruses.

The compounds of this invention are also useful in treating parasite, yeast and fungal infections, where such yeast and fungi are sensitive to upregulation by TNF or will elicit TNF production *in vivo*. A preferred disease state for treatment is fungal meningitis.

Compounds of the invention may also suppress neurogenic inflammation through elevation of cAMP in sensory neurones. They are, therefore, analgesic, anti-tussive and anti-hyperalgesic in inflammatory diseases associated with irritation and pain.

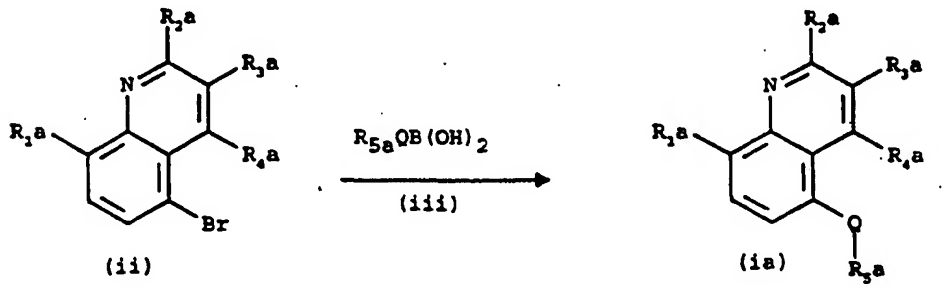
The compounds of formula (i) are preferably in pharmaceutically-acceptable form. By pharmaceutically-acceptable form is meant, *inter alia*, of a pharmaceutically-acceptable

level of purity excluding normal pharmaceutical additives such as diluents and carriers, and including no material considered toxic at normal dosage levels. A pharmaceutically-acceptable level of purity will generally be at least 50% excluding normal pharmaceutical additives, preferably 75%, more preferably 90% and still more preferably 95%.

The invention further provides a process for the preparation of a compound of formula (i), in which R_1 etc. are as defined above. It will be appreciated that functional groups such as amino, hydroxyl or carboxyl groups present in the various compounds described below, and which it is desired to retain, may need to be in protected forms before any reaction is initiated. In such instances, removal of the protecting group may be the final step in a particular reaction sequence. Suitable protecting groups for such functionality will be apparent to those skilled in the art. For specific details, see Protective Groups in Organic Synthesis, Wiley Interscience, TW Greene. Thus the process for preparing compounds of formula (i) in which R_3 contains an -OH group comprises deprotecting (for example by hydrogenolysis or hydrolysis) a compound of formula (i) in which R_3 contains an appropriate -OP wherein P represents a suitable protecting group (e.g. benzyl or acetyl).

It will be appreciated that where a particular stereoisomer of formula (i) is required, this may be obtained by conventional resolution techniques such as high performance liquid chromatography or the synthetic processes herein described may by performed using the appropriate homochiral starting material.

A process for the preparation of a compound of formula (i) comprises reaction of a bromide of formula (ii) with a suitably substituted aryl or heteroaryl portion, for example an aryl or heteroarylboronic acid of formula (iii)



wherein R_{1a} represents R_1 as defined in relation to formula (i) or a group convertable to R_1 and R_{2a}-R_{5a} similarly represent R_2-R_5 or groups convertable to R_2-R_5 respectively; and thereafter, if required, converting any group R_{1a} to R_1 and/or R_{2a} to R_2 and/or R_{3a} to R_3 and/or R_{4a} to R_4 and/or converting any group R_{5a} to R_5. Alternatively, a bromide of formula (ii) may be converted into the corresponding boronic acid (using standard conditions known to those skilled in the art) and this may be coupled with an aryl or heteroaryl halide, preferably a bromide.

This coupling reaction may be carried out under any standard conditions known to those skilled in the art, for example conditions described by Trecourt *et al, J. Het. Chem.* (1995) 32 1261, and references cited therein. The preparation of bromides of formula (ii) is described in WO-A-9744036. Boronic acids of formula (iii) are commercially available, previously described compounds, or are prepared using standard conditions known to those skilled in the art.

A compound of formula (i) may also be prepared by interconversion of other compounds of formula (i). For example, a compound in which R_5 contains a carboxylic acid may be prepared by appropriate hydrolysis of a compound in which R_5 contains an alkoxycarbonyl group (for example a methoxycarbonyl group).

Compounds in which R_2-R_4 contain a CO group, e.g. CO-alkyl, CO-aryl, CO-heteroaryl, CO-alkylaryl, CO-alkylheteroaryl or CO-alkylheterocyclo, may be prepared from compounds in which R_2-R_4 contain a CN group, by addition of a suitable organometallic agent (such as a Grignard reagent).

By way of further example, compounds in which R_2-R_4 contain an oxime may be prepared from compounds in which R_2-R_4 contain a carbonyl group. This transformation may be carried out using any appropriate standard conditions known to those skilled in the art. Compounds of formula (i) in which R_2-R_4 contain a carbonyl group may be reduced using standard conditions known to those skilled in the art (for example with sodium borohydride in an appropriate solvent) to provide compounds in which R_2-R_4 contains an alcohol group. Compounds in which R_2-R_4 is alkyl may be prepared by reduction of compounds in which R_2-R_4 is CO-alkyl using standard conditions known to those skilled in the art (for example hydrazine hydrate in the presence of a suitable base in an appropriate solvent). Other transformations may be carried out on compounds of formula (i) in which R_2-R_4 contains a carbonyl group. Such transformations include, but are not

limited to, reductive amination and alkylation. Any of the above transformations may be carried out either at the end of the synthesis or on an appropriate intermediate.

A compound of formula (i) or where appropriate a pharmaceutically-acceptable salt thereof and/or a pharmaceutically-acceptable solvate thereof, may be administered *per se* or, preferably, as a pharmaceutical composition also comprising a pharmaceutically-acceptable carrier.

Accordingly, the present invention provides a pharmaceutical composition comprising a compound of formula (i) or where appropriate a pharmaceutically-acceptable salt thereof and/or a pharmaceutically-acceptable solvate thereof, and a pharmaceutically-acceptable carrier.

The active compound may be formulated for administration by any suitable route, the preferred route depending upon the disorder for which treatment is required, and is preferably in unit dosage form or in a form that a human patient may administer to himself in a single dosage. Advantageously, the composition is suitable for oral, rectal, topical, parenteral administration or through the respiratory tract. Preparations may be designed to give slow release of the active ingredient.

The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats, etc, the compounds of the invention are effective in the treatment of humans.

The compositions of the invention may be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, suppositories, reconstitutable powders, or liquid preparations such as oral or sterile parenteral solutions or suspensions. Topical formulations are also envisaged where appropriate.

In order to obtain consistency of administration it is preferred that a composition of the invention is in the form of a unit dose.

Unit dose presentation forms for oral administration may be tablets and capsules and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers for example microcrystalline cellulose, lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate; disintegrants, for example starch,

polyvinylpyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically-acceptable wetting agents such as sodium lauryl sulphate.

The solid oral compositions may be prepared by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers.

Such operations are of course conventional in the art. The tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating.

Oral liquid preparations may be in the form of, for example, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia, non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

Compositions may also suitably be presented for administration to the respiratory tract as a snuff or an aerosol or solution for a nebuliser, or as a microfine powder for insufflation, alone or in combination with an inert carrier such as lactose. In such a case the particles of active compound suitably have diameters of less than 50 μm, such as from 0.1 to 50 μm, preferably less than 10 μm, for example from 1 to 10 μm, 1 to 5 μm or from 2 to 5 μm. Where appropriate, small amounts of other anti-asthmatics and bronchodilators for example sympathomimetic amines such as isoprenaline, isoetharine, salbutamol, phenylephrine and ephedrine; corticosteroids such as prednisolone and adrenal stimulants such as ACTH may be included.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, and, depending on the concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilised before filling into a suitable vial or ampoule and sealing.

Advantageously, adjuvants such as local anaesthetic, a preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The compositions may contain from 0.1% to 99% by weight, preferably from 10-60% by weight, of the active material, depending on the method of administration.

Compounds of formula (i), or if appropriate a pharmaceutically-acceptable salt thereof and/or a pharmaceutically-acceptable solvate thereof, may also be administered as a topical formulation in combination with conventional topical excipients.

Topical formulations may be presented as, for instance, ointments, creams or lotions, impregnated dressings, gels, gel sticks, spray and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams. The formulations may contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions.

Suitable cream, lotion, gel, stick, ointment, spray or aerosol formulations that may be used for compounds of formula (i) or if appropriate a pharmaceutically-acceptable salt thereof, are conventional formulations well known in the art, for example, as described in standard text books such as Harry's Cosmeticology published by Leonard Hill Books, Remington's Pharmaceutical Sciences, and the British and US Pharmacopoeias.

Suitably, the compound of formula (i), or if appropriate a pharmaceutically-acceptable salt thereof, will comprise from about 0.5 to 20% by weight of the formulation, favourably from about 1 to 10%, for example 2 to 5%.

The dose of the compound used in the treatment of the invention will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and the relative efficacy of the compound. However, as a general guide suitable unit doses may be 0.1 to 1000mg, such as 0.5 to 200, 0.5 to 100 or 0.5 to 10mg, for example 0.5, 1, 2, 3, 4 or 5mg; and such unit doses may be administered more than once a day, for example 2, 3, 4, 5 or

6 times a day, but preferably 1 or 2 times per day, so that the total daily dosage for a 70kg adult is in the range of about 0.1 to 1000mg, that is in the range of about 0.001 to 20 mg/kg/day, such as 0.007 to 3, 0.007 to 1.4, 0.007 to 0.14 or 0.01 to 0.5mg/kg/day, for example 0.01, 0.02, 0.04, 0.05, 0.06, 0.08, 0.1 or 0.2 mg/kg/day, and such therapy may extend for a number of weeks or months.

When used herein the term "pharmaceutically-acceptable" encompasses materials suitable for both human and veterinary use.

The following Example illustrates the invention.

Example **8-Methoxy-2-methyl-5-phenylquinoline**

5-Bromo-8-methoxy-2-methylquinoline (509 mg) and benzene boronic acid (323 mg) were added to a mixture of 2 M aqueous potassium carbonate (2 ml), toluene (10 ml) and ethanol (1 ml) and refluxed for 30 minutes under a nitrogen atmosphere. The mixture was cooled, triphenylphosphine (75 mg) and dichlorobis(triphenylphosphine)palladium chloride (66 mg) were added and the mixture was heated at 60°C overnight. After cooling, the reaction mixture was diluted with ethyl acetate (30 ml). The organic phase was washed with 2 M aqueous potassium carbonate solution (2 x 30 ml), dried (magnesium sulphate), filtered and evaporated *in vacuo* to give the title compound (272 mg) as an off-white solid.

TLC R_f 0.26 (dichloromethane)

mp 133-134°C

Assay methods

The assays used to confirm the phosphodiesterase IV inhibitory activity of compounds of formula (i) are standard assay procedures as disclosed by Schilling *et al*, Anal. Biochem. 216:154 (1994), Thompson and Strada, Adv. Cycl. Nucl. Res. 8:119 (1979) and Gristwood and Owen, Br. J. Pharmacol. 87:91P (1986).

Compounds of formula (i) have exhibited activity at levels consistent with those believed to be useful in treating phosphodiesterase IV-related disease states in those assays.

The ability of compounds of formula (i) to inhibit TNF production in human peripheral blood mononuclear cells (PMBC's) is measured as follows. PMBC's are prepared from freshly taken blood or "Buffy coats" by standard procedures. Cells are plated out in RPMI1640 +1% foetal calf serum in the presence and absence of inhibitors.

LPS (100 ng/ml) is added and cultures are incubated for 22 h at 37°C in an atmosphere of 95% air/5% CO_2. Supernatants are tested for TNFα by ELISA using commercially available kits.

In vivo activity in a skin eosinophilia model is determined by using the methods described by Hellewell *et al*, Br. J. Pharmacol. 111:811 (1994) and Br. J. Pharmacol. 110:416 (1993). Activity in a lung model is measured using the procedures described by Kallos and Kallos, Int. Archs. Allergy Appl. Immunol. 73:77 (1984), and Sanjar *et al*, Br. J. Pharmacol. 99:679 (1990).

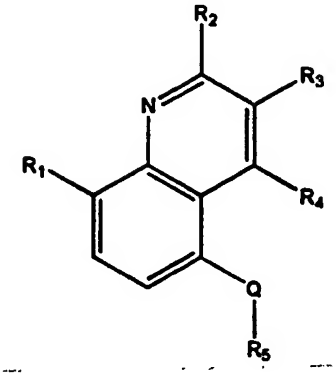
An additional lung model, which allows measurement of inhibition of the early and late-phase asthmatic responses and also the inhibition of airway hyperreactivity, is described by Broadley *et al*, Pulmonary Pharmacol. 7:311 (1994), J. Immunological Methods 190:51 (1996) and British J. Pharmacol. 116:2351 (1995).

Abbreviations

LPS	Lipopolysaccharide (endotoxin)
ELISA	Enzyme linked immunosorbent assay

CLAIMS

1. A compound for use in therapy, of the general formula (i)



(i)

wherein R_1 represents C_{1-6} alkoxy (alkyl portion optionally substituted with one or more halogens) or thioalkyl;

R_2, R_3 and R_4, which may be the same or different, represent H, OR_{11}, COR_7, CN, CO_2R_8, $C(=NOR_7)R_7$, alkyl-$C(=NOR_7)R_7$, halogen, CF_3, $CONR_{12}R_{13}$, NR_9R_{10} or R_7;

R_5 represents H or a substituent selected from halogen, arylalkyl, heteroarylalkyl, heterocycloalkyl, alkyl, hydroxy, alkoxy, CO_2R_8, $SO_2NR_{12}R_{13}$, $CONR_{12}R_{13}$, -CN, NR_9R_{10}, COR_{11} and $S(O)_nR_{11}$;

R_7 represents H, alkyl, cycloalkyl, aryl, heteroaryl, heterocyclo, arylalkyl, heteroarylalkyl or heterocycloalkyl, any of which may be optionally substituted at any position with R_{16};

R_8 represents H, alkyl, arylalkyl, heteroarylalkyl or heterocycloalkyl;

R_9 represents alkylcarbonyl, alkoxycarbonyl, arylsulphonyl, heteroarylsulphonyl, heterocyclosulphonyl, arylcarbonyl, heteroarylcarbonyl, heterocyclocarbonyl or alkylsulphonyl and R_{10} represents H or R_{11}, or NR_9R_{10} represents a heterocyclic ring optionally substituted with one or more R_{15};

R_{11} represents alkyl, cycloalkyl, aryl, heteroaryl, heterocyclo, arylalkyl, heteroarylalkyl or heterocycloalkyl;

R_{12} and R_{13}, which may be the same or different, each represent R_7, or $NR_{12}R_{13}$ represents a heterocyclic ring optionally substituted with one or more R_{15};

R_{15} represents alkyl, arylalkyl or heteroarylalkyl;

R_{16} represents halogen, hydroxy, OR_{11}, NR_9R_{10}, CN, CO_2H, CO_2R_{11}, $CONR_{12}R_{13}$ or COR_{11};

n represents 0-2; and

Q represents an aryl or heteroaryl ring, attached through any appropriate atom and optionally substituted at any position(s) with one or more substituents R_5;

or a pharmaceutically-acceptable salt thereof;

provided that Q is not a bicyclic system in which a 5-membered ring including a N atom is attached to the quinoline nucleus at the 2-position and fused to a 6-membered ring at the 4,5-positions.

2. A compound of formula (i) as defined in claim 1, independent of use, excluding 5,5'-bis(8-methoxyquinoline), 5,5'-bis(8-methoxyquinaldine), 1-(8-ethoxy-5-quinolyl)-3,4-dihydroisoquinoline, 1-(8-ethoxy-5-quinolyl)isoquinoline, 2-(8-ethoxy-5-quinolyl)-1,2,3,4-tetrahydroisoquinoline, 8-isopropoxy-5-(1-naphthyl)quinoline, 5-methoxy-8-phenylquinoline, 5-methoxy-8-[2-(t-butylcarbonylamino)phenyl]quinoline and 5-methoxy-8-[2-(t-butylcarbonylamino)-5-methoxyphenyl]quinoline.

3. A compound of claim 1 or claim 2, wherein R_1 is alkoxy optionally substituted with one or more halogens.

4. A compound of any preceding claim, wherein R_2 is H, alkyl, CF_3 or alkoxyalkyl.

5. A compound of any preceding claim, wherein R_3 and/or R_4 is H.

6. A compound of any preceding claim, wherein R_5 is H, CO_2R_8 or $CONR_{12}R_{13}$.

7. A compound of any preceding claim, wherein Q is monocyclic.

8. A compound of claim 7, wherein Q is phenyl or pyridyl.

9. A compound of claim 1, which is 8-methoxy-2-methyl-5-phenylquinoline.

10. A pharmaceutical composition for therapeutic use comprising a compound of any preceding claim and a pharmaceutically-acceptable carrier or excipient.

11. Use of a compound of any of claims 1 to 9, for the manufacture of a medicament for use in the treatment of a disease state capable of being modulated by inhibition of phosphodiesterase IV or Tumour Necrosis Factor, a pathological condition associated with a function of phosphodiesterase IV, eosinophil accumulation or a function of the eosinophil.

12. The use of claim 11, wherein the disease state is an inflammatory disease or autoimmune disease.

13. The use of claim 11, wherein the disease state is selected from asthma, chronic bronchitis, chronic pulmonary inflammatory disease, chronic obstructive airways disease, atopic dermatitis, allergic rhinitis, psoriasis, arthritis, rheumatoid arthritis, joint inflammation, ulcerative colitis, Crohn's disease, atopic eczema, stroke, bone resorption disease, multiple sclerosis and inflammatory bowel disease.

14. The use of claim 11, wherein the disease state is selected from urticaria, allergic conjunctivitis, vernal conjunctivitis, inflammation of the eye, allergic responses in the eye, eosinophilic granuloma, gouty arthritis and other arthritic conditions, adult respiratory distress syndrome, diabetes insipidus, keratosis, cerebral senility, multi-infarct dementia, senile dementia, memory impairment associated with Parkinson's disease, depression, cardiac arrest, intermittent claudication, rheumatoid spondylitis, osteoarthritis, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, acute respiratory distress syndrome, cerebral malaria, silicosis, pulmonary sarcoidosis, reperfusion injury, graft vs host reaction, allograft rejection, infection-related fever or myalgia, malaria, HIV, AIDS, ARC, cachexia, keloid formation, scar tissue formation, pyresis, systemic lupus erythematosus, type 1 diabetes mellitus, Bechet's disease, anaphylactoid purpura nephritis, chronic glomerulonephritis, leukaemia, tarditive dyskinesia, yeast or fungal infection, conditions requiring gastroprotection, and neurogenic inflammatory disease associated with irritation and pain.

15. The use of claim 12, wherein the disease state is asthma.

16. The use of claim 12, wherein the disease state is chronic obstructive airways disease or chronic bronchitis.

INTERNATIONAL SEARCH REPORT

Int onal Application No
PCT/GB 98/01770

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D215/26 A61K31/47

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimumdocumentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 105, no. 19, 10 November 1986 Columbus, Ohio, US; abstract no. 172254p, ASHAKS, J. ET AL: "8-Mercaptoquinoline(thiooxine) and its derivatives. ..." XP002057449 * RN 104711-54-8 * see abstract & CHEM. PAP., vol. 39, no. 5, - 1985 pages 667-686, ---	1
A	WO 93 07146 A (SYNTEX (U.S.A.) INC.) 15 April 1993 see claims --- -/--	1,7,8

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publicationdate of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of theinternational search	Date of mailing of the international search report
21 September 1998	02/10/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Van Bijlen, H

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int. ional Application No
PCT/GB 98/01770

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94 22852 A (SYNTEX (U.S.A.) INC.) 13 October 1994 see claims	1,7,8
P,A	WO 97 44036 A (CHIROSCIENCE LTD.) 27 November 1997 see claims	1,7,8
P,A	WO 97 44322 A (CHIROSCIENCE LTD.) 27 November 1997 see claims	1,7,8

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int[illegible]onal Application No
PCT/GB 98/01770

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9307146 A	15-04-1993	AU 670544 B	25-07-1996
		AU 2781592 A	03-05-1993
		CA 2117059 A	15-04-1993
		EP 0612321 A	31-08-1994
		ES 2105920 A	16-10-1997
		FI 941567 A	06-04-1994
		HU 66969 A	30-01-1995
		HU 9500113 A	28-06-1995
		IL 103388 A	30-09-1997
		JP 7500321 T	12-01-1995
		MX 9205794 A	01-04-1993
		NO 941210 A	05-04-1994
		NZ 244660 A	26-05-1995
		PT 100938 A	29-10-1993
		US 5716954 A	10-02-1998
		ZA 9207755 A	08-04-1994
WO 9422852 A	13-10-1994	US 5455252 A	03-10-1995
		AT 170855 T	15-09-1998
		AU 679222 B	26-06-1997
		AU 6412994 A	24-10-1994
		CA 2159603 A	13-10-1994
		EP 0691966 A	17-01-1996
		FI 954651 A	29-09-1995
		HU 9500111 A	28-06-1995
		HU 73181 A	28-06-1996
		JP 8511238 T	26-11-1996
		NO 953879 A	22-11-1995
		NZ 263436 A	22-08-1997
WO 9744036 A	27-11-1997	AU 2905897 A	09-12-1997
		AU 2905997 A	09-12-1997
		WO 9744322 A	27-11-1997
		US 5804588 A	08-09-1998
WO 9744322 A	27-11-1997	AU 2905897 A	09-12-1997
		AU 2905997 A	09-12-1997
		WO 9744036 A	27-11-1997
		US 5804588 A	08-09-1998